PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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December 6, 2011

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Dear Dr. White,

The following comments are submitted on behalf of the more than three million members and supporters of People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) in response to the nominations of substances to NTP for study in 2011 (Federal Register 76(214): 68461). Our organizations are committed to using the best available science to protect animals from suffering in laboratory experiments and promote the acceptance of human-relevant methods for risk assessment.

We are encouraged that for the most part, NTP appears to have endeavored to minimize animal use in its selection and consideration of the current nominations. Each nomination originated from publicly-accountable health agencies rather than from unidentified private individuals; each Chemical Information Review Document contains a thorough, documented literature search and a rigorous discussion of structure-activity relationships; and each Research Concept uses a tiered testing strategy.

We are, however, concerned that non-animal approaches do not appear to have been fully considered for sulfolane and that *in vivo* tests for at least one phenolic benzotriazole are already planned.

Trimethylsilyldiazomethane (TMSD) was nominated by the Occupational Safety and Health Administration (OSHA) following the deaths of two chemists who were exposed in the workplace. Notably, the Research Concept considers the purity and stability of TMSD from different sources, the effects of the carrier/vehicle on toxicity, the feasibility of generating a specified atmospheric concentration of TMSD vapor in an inhalation chamber without animals, and the stability of TMSD in artificial lung fluid. Appropriately, if TMSD is found to readily form diazomethane, which has been shown previously to be highly toxic and for which an occupational exposure limit is already established, then an acute inhalation toxicity study should not be conducted.

Sulfolane was nominated by the State of Alaska Department of Environmental Conservation (ADEC) due to concern over groundwater contamination originating from the Flint Hills Resources North Pole Refinery (NPR). Sulfolane from the NPR has been detected in nearly 300 drinking water wells, and ADEC is responsible for determining appropriate cleanup levels to be used for site remediation.

It should be emphasized that the primary source of sulfolane in the groundwater at the refinery is believed to be historic releases of wastewater and fuel which began in 1985 and that a network of monitoring wells has been installed to ensure that concentrations are no longer increasing. Earlier this year, the Agency for Toxic Substances and Disease Registry (ATSDR) recommended a public health action level for chronic exposure to sulfolane in water of 20 parts per billion (ppb) for infants and 70 ppb for adults. These values were derived from a 1987 study report which lacked details on dosing and parameter variability, and they are being disputed by ToxStrategies, a contractor for the site's potentially responsible party. In a letter to the National Institutes of Health, Luke T. Hopkins, the Mayor of Fairbanks North Star Borough, Alaska

disagrees with ToxStrategies' approach and supports ATSDR's lower recommended levels based on a precautionary principle. While additional toxicity data may support these recommendations, it seems that the only obstacle preventing their immediate acceptance is a dispute with the responsible party.

Although the Research Concept for sulfolane proposes a tiered testing strategy to reduce the number of animals used, it is entirely animal-based. Consideration must be given to the use of non-animal approaches to further reduce the number of animals used.

Phenolic Benzotriazoles (PBZTs) appear to be a lower priority for further study since toxicity data exist for several of the chemicals within this class. In addition, several PBZTs are already regulated by the Environmental Protection Agency (EPA) as inert ingredients in pesticides and by the Food and Drug Administration as food contact substances.

Four PBZTs, drometrizole, octrizole, DitPe-BZT, and DiMeEtPh-BZT, comprised the Phenolic Benzotriazoles Category in EPA's High Production Volume chemical testing program for which a test plan was submitted in 2001. The category justification was based on the similarity of the structural backbone and the regular pattern of chemical, physical, and toxicological properties of all members. In its comments, EPA judged the grouping to be adequately supported. Notably, although the sponsor initially proposed testing for reproductive toxicity for drometrizole and DiMeEtPh-BZT, EPA suggested that adequate evaluation of reproductive organs from available repeated-dose studies and the availability of developmental toxicity studies might satisfy the reproductive/developmental toxicity endpoints. This would seem to indicate a relatively low level of concern. In response, the sponsor summarized data showing no effects on reproductive organs in repeated-dose tests for drometrizole, DitPe-BZT, and DiMeEtPh-BZT as well as no effects on implantation rates, no embryotoxicity and no teratogenic effects for drometrizole and DiMeEtPh-BZT in developmental toxicity tests.

The Research Concept proposes to evaluate up to twenty-nine PBZTs using short term *in vitro* studies in order to prioritize chemicals for further testing. We are concerned that selected PBZTs will also be evaluated for developmental and/or subchronic toxicity in parallel to these *in vitro* assays. In particular, the Research Concept identifies DitPe-BZT since it has "indications of reproductive toxicity." This apparently refers to increases in testes weights reported in a 90-day study on rats which is among those mentioned above. The study summary states that this effect was largely a result of decreases in body weight and not judged to be of toxicological significance (http://www.epa.gov/hpv/pubs/summaries/phenbenz/c13266tl.pdf). The Research Concept also states that DiMeEtPh-BZT reduced fetal weights and delayed skeletal maturation at the mid-dose in the absence of maternal toxicity in a developmental toxicity study. Again, the Research Concept fails to mention that in the absence of effects in the high dose group, these effects were considered incidental to treatment. The concern over potential reproductive and developmental effects thus appears to be overstated and all PBZTs should be evaluated *in vitro* before any further testing is even considered.

Thank you for your attention to these comments. I can be reached at (757) 622-7382, ext. 8001, or by e-mail at josephm@peta.org.

Sincerely,

REDACTED

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People for the Ethical Treatment of Animals